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EVOLUTIONARY THEORY AND STUDIES OF MODEL ORGANISMS PREDICT A CAUTIOUSLY POSITIVE PERSPECTIVE ON THE THERAPEUTIC USE OF HORMESIS FOR HEALTHY AGING IN HUMANS

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□ Hormesis, the beneficial effects of mild stress exposures, is a well documented phenomenon in a range of organisms. The documentation mainly relies on relatively simple and controlled laboratory investigations. In order to better understand hormesis and predict the outcome of more complex and realistic conditions, a number of key issues should be investigated in much more detail. One obstacle is the development of precise treatments optimized for single individuals. Only then can we progress with the use of hormesis as a therapeutic tool for humans.

Key words: Evolution, Multiple Stressors, Sex specific, Stress Response

INTRODUCTION

Hormesis is a 'stimulatory effect of low doses of substances or treatments known to be toxic or harmful at higher doses' (see Calabrese *et al.* 2007). This phenomenon is found across plant and animal species and is induced by multiple stress factors, which has promoted the idea of using it for therapeutic purposes, especially for increasing human health- and life span. Beneficial effects have been reported for e.g. growth, longevity and resistance to severe stress (Le Bourg and Rattan 2008; Calabrese and Blain 2009). The hormetic effects may last much longer than the vast majority of the stress induced changes in e.g. metabolites and gene expression (Sørensen *et al.* 2005; Malmendal *et al.* 2006) and it is unclear how this biological effect is preserved.

Mechanisms promoting hormesis

The main explanation for the occurrence of hormesis is the stimulation of genes and processes in response to stress agents. Candidate genes

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are those ensuring metabolic efficiency or performing various house keeping functions, including oxidative stress scavengers, DNA repair systems and the heat shock proteins (Hsps) (Rattan 2004; Le Bourg and Rattan 2008).

Evolutionary predictions concerning hormesis

Evolutionary theory predicts that organisms evolve protective systems against damaging conditions to maintain high fitness in environments that are variable in time and space. As such, it is predicted that natural selection, if unconstrained, will ensure high average fitness, leaving little room for further improvement (by e.g. hormesis) for a given population in its particular environment. Following this line of reasoning, little hormesis is expected to occur for fitness traits in natural populations (Forbes 2000).

Still, the hormesis phenomenon might be relevant within specific time intervals and for individual traits (especially life span). Moreover, hormesis might be relevant for organisms living in benign environments, e.g. humans in industrialized countries, domesticated animals and cultivated plants. From an evolutionary point of view it could be argued that these organisms currently experience less stress than through most of their evolutionary history, and thus have a potential benefit that might be available with little associated cost (Parsons 2000; Parsons 2003).

PERSPECTIVES FOR THE THEARAPEUTIC USE OF HORMESIS

Hormetic mechanisms most likely have evolved to maintain homeostatic or homeodynamic functioning of the organism in response to perturbation by fluctuating environmental conditions. Work so far suggests that hormesis acts through a combination of mechanisms - some shared among stress types and some stress specific. We need to collect further knowledge about the mechanisms promoting hormesis to figure out when, in which traits and under which conditions hormesis can be expected to occur. Model organisms, such as *Drosophila* and *Caenorhabditis elegans*, play an important role for research in this area with short generation times, easily obtainable large sample sizes and with well known and/or manipulated genetic backgrounds. Also ethical considerations are affecting the choice of experimental organism. Combined with biological theory the results obtained with model organisms could potentially lead to a better understanding of the hormesis phenomenon and factors involved in aging. Ultimately, the hypotheses generated by such investigations could be applied to other organisms including humans. However, so far the results suggest a complicated pattern that will not easily be transferred to actual treatments in humans.

Predicting appropriate dosage

The stress level needed to achieve an optimal hormetic response is expected to be a quite narrow window in most cases and threshold levels for hormesis can vary between experiments (Minois 2000; Norry and Loeschcke 2003; Landis *et al.* 2004; Wang *et al.* 2004; Bubliy and Loeschcke 2005). Further, the effects of a hormetic stimulation are known to interact with environments, stress types, species, sexes, life stages, genotypes and populations (see e.g. Sørensen *et al.* 2008). Furthermore, the exact application of the stress (e.g. the combination of timing, strength and duration) can have a large impact. Thus, we have very limited predictive power as to whether certain stimulations will be beneficial to an individual with unknown genetic and environmental background, i.e. we can not predict the beneficial dosage precisely. This is of concern as too high a stimulation will lead to decreased performance, i.e. it must be ensured that benefits are larger than costs associated with mild stress. This implies that thorough and extensive experimental work is needed to reach a sufficient understanding to avoid negative effects of a treatment.

Different responses in males and females

Sex specific hormetic effects on life span are common in *Drosophila*, with the beneficial effects of mild stress often appearing to be larger in males than in females. The phenomenon does exist in both sexes, but females may have a different sensitivity and/or hormesis is induced by partly different mechanisms (Le Bourg *et al.* 2001; Hercus *et al.* 2003). This difference may relate to the reproductive status of the organism as females in contrast to males have to trade off stress resistance and reproduction (Salmon *et al.* 2001). Reduced reproduction in individuals exposed to mild stress (Krebs and Loeschcke 1994) may be partly responsible for the hormetic effect on longevity and later exposure to severe stresses – because more energy is invested in body maintenance in mildly stressed individuals.

The effect of multiple stress factors

So far most studies have addressed the hormetic effect of single stress agents. This is an artificial situation since all species are challenged by multiple stressors of both natural and anthropogenic origin. The effects of multiple stressors may produce combined effects larger than expected from the isolated effects (potentiation, positive synergism) or may counteract and perhaps cancel out (antagonism) as shown for some model organisms (Bindesbøl *et al.* 2005; Holmstrup *et al.* 2008). Research in this area is still rather limited and little is known about how combined effects of multiple stressors influence the occurrence and magnitude of hormesis.

CONCLUSIONS

During the last century we have seen a dramatic increase in the average expected life span of humans in the industrial parts of the world, as the standard of living and the quality of medical care has been improved. One possible avenue to further increased life- and health span is through hormetic treatment.

To apply hormetic treatments as a therapy, we need to develop methods to estimate or measure the individual stress history and tools that can predict the appropriate hormetic dose needed on an individual basis, similar to the idea for other types of medication. Most, if not all, experiments addressing hormesis report responses as population averages. However, any hormetic treatment would rely on complex cost-benefit relations that rely on individual conditions. This is important if we want to use hormesis as a therapeutic treatment in humans, as the appropriate level of stress might depend on both the genetic background as well as the environment of the organism. Too high levels of stress will lead to damaging effects and thus potentially decreased life span.

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